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FIRST PERSON

First person – Rafael José Argüello

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping early-career researchers promote themselves alongside their papers. Rafael José Argüello is the first author on 'SunRiSE – measuring translation elongation at single-cell resolution by means of flow cytometry', published in Journal of Cell Science. Rafael is a researcher in the lab of Philippe Pierre at Centre d'Immunologie de Marseille-Luminy, Marseille, France, investigating tRNAs and translation, and the regulation of energetic metabolism in the context of infection and cancer.

Rafael José Argüello

How would you explain the main findings of your paper in lay terms?

This paper describes the development of a novel technique to monitor the speed at which proteins are produced in single cells. The process of protein synthesis is called translation and is performed by the 'translation machinery', consisting of transfer RNAs (tRNAs), ribosomes and messenger RNAs (mRNAs). Some years ago in Philippe Pierre and Evelina Gatti's laboratory, Enrico Schmidt and colleagues developed a method called 'SUnSET', to take a snapshot of the number of ribosomes engaged in translation. As in any snapshot, however, this method does not give any information regarding the dynamics and velocity of the translating ribosomes moving along the mRNAs to produce proteins. To understand the principle of our new method, 'SunRiSE', imagine that cars are moving onto a long bridge. To monitor speed, our method uses a drug that acts as a gate and blocks the 'initiation' or 'entry' of new cars (ribosomes) onto the bridge (mRNA), and leaves the ones already in place to proceed as they were. We then take a snapshot of the situation every 30 s and determine the amount of cars remaining on the bridge. If the number is constant, it means that they are still or stuck in a traffic jam. By contrast, if the number decreases very fast, it means that the cars are advancing towards the end of the bridge very fast. The faster they go, the more rapidly the traffic should clear. Now imagine that each cell has its own set of cars/ribosomes, but the drug that blocks the entrance to the bridge appears at the same time for all cells. One advantage of our method is that we can determine, in parallel, the speed of the processing ribosomes of each different cell type or cell state that is present in a sample. For that reason, and due to its simplicity, SunRiSE is particularly interesting for researchers who want to study protein translation in patient blood samples or animal models. The sensitivity of SunRiSE allows analysis of rare cells that are difficult or even impossible to study with other techniques.

Were there any specific challenges associated with this project? If so, how did you overcome them?

This story began when analysing flow cytometry snapshots from SUnSET data with my friend and former colleague, the excellent wine maker Dr Alexandre Dalet. When looking at the number of ribosomes that were engaged in translation after transfecting cells with viral dsRNA, we observed that while most cells blocked their protein synthesis, a small proportion often showed higher levels of ribosome engagement. We wondered if the ribosomes in those cells were elongating or if they were simply stuck on mRNAs, like the traffic jam of cars previously mentioned. Owing to the low frequency of those cells, we couldn't answer that question using classical biochemical bulk analysis. To solve this challenge, some time later, after Alexandre had left the lab, I had the idea of adapting classical ribosome run-off experiments for flow cytometry. This allowed us to focus on some minor cell populations and obtain our answer. In the end, the method proved to be useful for our scientific community and we tested it in different applications. One of the biggest challenges after the development of the method was to find a catchy name for it. I thought that, as the method evolved from the SUnSET technique, an appropriate name (because it follows the logical order of astronomical events) was SUnSET-based ribosome speed of elongation (SunRiSE).

When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?

"I felt 'eureka', not because I was right, but because I was not wrong any more."

'Eureka' is not something I say out loud or feel when an experiment confirms my hypothesis. Instead, I felt 'eureka' when I found out that I was completely wrong when thinking that those cells with high levels of engaged ribosomes upon viral dsRNA transfection were stalled in translation. I felt 'eureka', not because I was right, but because I was not wrong any more. That is the beauty of science, we must change our minds in face of the evidence. Nature and experiments direct us towards what to believe; it does not matter whether your hypothesis is correct or incorrect, in the end we all arrive at the same conclusion.

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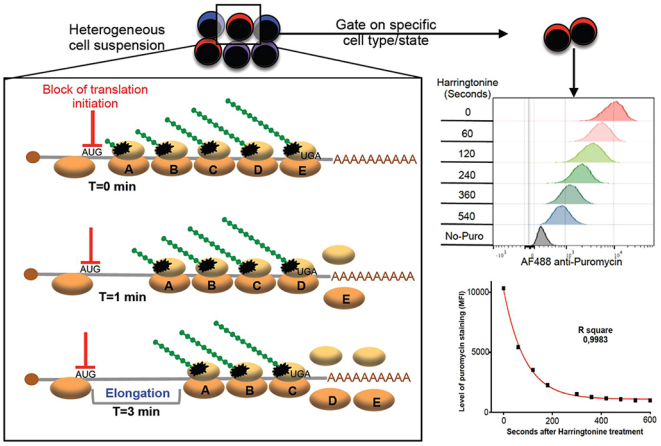

The SunRiSE technique is adapted for flow cytometry, and its beauty lies in its multi-parametric capacity. By using SunRiSE we can analyse the amount and speed of translation in activated T and B cells in parallel, gating for cells with different numbers of rounds of cell division (for more detail see Fig. S2 of the article).

Why did you choose Journal of Cell Science for your paper?

I chose Journal of Cell Science because it has the first author section, which might help young and motivated researchers to meet other young and motivated researchers or inspire them to come to our lab to do a PhD or a postdoc. Moreover, it is a renowned journal with high quality articles and the right readership for our work.

Have you had any significant mentors who have helped you beyond supervision in the lab?

I feel that I am very lucky, because I have always found mentors that changed my life. Dr Gabriel Gellon (founder of Expedición Ciencia) has the ability to make dreams contagious, and I learned that if you have a good dream and you have the talent to make it contagious, then in the future you will find yourself having fun, and working surrounded by people who have the same conviction. My scientific mentor is Dr Ruben P. Laguens, an artist and scientist, a passionate experimental pathologist who maintained his curiosity and knowledge through several decades of doing research. Beyond supervision in the lab, I have had the luck to experience the advice and help of Dr Eduardo Gaddi at the Pedro de Elizalde Kids Hospital and Pierre Golstein at the Centre d'Immunologie de Marseille-Luminy. I will always try to find occasions to thank those people who helped me without looking for anything in exchange.

What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?

The pleasure that I felt when I started to understand and learn how nature works was incredible. Since the beginning of my career, I have been involved in science teaching and educational projects because I wanted to offer others the opportunity to feel the same. The joy in understanding, thinking and discovering was something that was 'unburied' from my brain during my first undergraduate molecular biology course, with the intellectual brain surgery performed by Dr Alberto Rodolfo Kornblihtt, who I consider my first professor. Alberto works on the impact of the speed of transcription and its effect on alternative splicing (one of his major discoveries) and it's not a coincidence that I now work on the impact of the speed of protein synthesis and folding.

What's next for you?

To continue doing research, science teaching and enjoying it.

Tell us something interesting about yourself that wouldn't be on your CV

I am a hitch-hiker scientist who plays underwater hockey and kitesurfs, and I like singing, even if I am not (at all) good at it. I like to have fun doing serious things with friends and colleagues.

Reference

Argüello, R. J., Reverendo, M., Mendes, A., Camosseto, V., Torres, A. G., Ribas de Pouplana, L., van de Pavert, S. A., Gatti, E. and Pierre, P. (2018). SunRiSE–measuring translation elongation at single-cell resolution by means of flow cytometry. *J. Cell Sci.* **131**, jcs214346.